UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,722	04/19/2000	DAVID J SQUIRRELL	124-765	3335

23117 7590 05/05/2005

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,722	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *107-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/2005 has been entered.

[2] Claims 107-135 are pending in the application.

[3] Applicants' amendment to the claims, filed 2/14/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's arguments filed 2/14/2005 have been fully considered.

Claim to Priority

[5] Applicants' claim for foreign priority under 35 USC § 119(a)-(d) to GB 9722481.0, filed 10/25/1997, is acknowledged. A certified copy of the foreign priority document was filed in the instant application on 4/19/2000.

Information Disclosure Statement

[6] An Information Disclosure Statement was filed on 4/19/2000. A copy of the corresponding Form PTO-1449 was attached to the Office action mailed 11/7/2000.

[7] If the examiner has inadvertently overlooked an IDS that has previously been filed in the instant application, applicants' cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Oath/Declaration

[8] It is noted that the originally filed declaration (filed 4/19/2000) listed inventor Rachel L. Price. A petition to change Inventor Price's name to Rachel L. Leslie was filed on 10/2/2002 with an accompanying substitute declaration.

Claim Objections

[9] Claims 107, 111, 120, 125, 128, 131, and 133 are objected to as being grammatically incorrect in the recitation of "temperatures of 37°C" (claim 107) and "mutations at amino acids 87 or 107" (claims 111, 120, 125, 128, 131, and 133). It is suggested that the term be replaced with, for example, "a temperature of 37°C" and "a mutation at amino acid 87 or 107." It is noted that the examiner has interpreted the term "mutations at amino acids 87 or 107" as reading "a mutation at amino acid 87 or 107." It is further noted that the examiner has interpreted the term "includes mutations at amino acids 87 or 107 in the sequence of *E. coli* adenylate kinase" as meaning that the *E. coli* adenylate kinase has mutation only at position 87 or 107 and no other mutation(s). If these interpretations are incorrect, applicants are requested to clarify the record.

[10] The phrase "group consisting of...or a Luciola luciferase" in claims 108, 120, and 123 is an improper alternative expression and should be replaced with, for example, "group consisting of...and a Luciola luciferase." See MPEP 2173.05(h).

[11] Claim 109 is objected to in the recitation of "the luciferase is selected from the group consisting of" and then recites only a single species of luciferase, i.e., "Luciola luciferase in which the amino acid at the 217 position is mutated to a hydrophobic amino acid." It is suggested that the term "...wherein the luciferase is selected from the group consisting of Luciola luciferase..." be replaced with, for example, "...wherein the luciferase is Luciola luciferase."

[12] Claim 128 is objected to in the recitation of "and expresses adenylate kinase and expresses adenylate kinase." It is suggested that applicants delete one of the occurrences of "and expresses adenylate kinase."

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claims 107-112, 115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 107 (claims 108-112 dependent therefrom), 120 (claims 121-122 dependent therefrom), and 128 (claims 129-130 dependent therefrom) are drawn to "[a]

method for producing a luciferase which is substantially free of *E. coli* adenylate kinase..." However, the claimed methods fail to achieve the desired result. The method may achieve luciferase that is "substantially free" of enzymatically active *E. coli* adenylate kinase. However, the *E. coli* adenylate kinase is still present with the luciferase, only in a denatured form. Thus, a skilled artisan practicing the claimed methods would recognize that the methods achieve only the denaturation of thermosensitive adenylate kinase and do not produce "luciferase which is substantially free of *E. coli* adenylate kinase." It is suggested that applicants clarify the meaning of the claims.

[b] The terms "Photinus pyralis luciferase which has a mutation at position 354" and "Luciola luciferase with a mutation at position 354" in claims 108, 115, 120 (claim(s) 121-122 dependent therefrom), and 123 (claim(s) 124 dependent therefrom), the term "Luciola luciferase in which the amino acid at the 217 position" in claims 109, 116, 128 (claim(s) 129-130 dependent therefrom), and 131, and the term "amino acids 87 or 107 in the sequence of *E. coli* adenylate kinase" in claims 111, 120 (claim(s) 121-122 dependent therefrom), 125 (claim(s) 126-127 dependent therefrom), 128 (claim(s) 129-130 dependent therefrom), 131 (claim(s) 132 and 134-135 dependent therefrom), and 133 are indefinite as it is unclear as to the reference sequences, i.e., the amino acid sequences of Photinus pyralis luciferase, Luciola luciferase, and *E. coli* adenylate kinase, that are referenced in the claims. It is suggested that applicants identify the intended sequences by a sequence identifier, i.e., "SEQ ID NO:". In the interest of advancing prosecution, the "Photinus pyralis luciferase" has been interpreted as having

the amino acid sequence of the Photinus pyralis luciferase as disclosed by Squirrell et al. (WO 96/22376, particularly pp. 20-24) and the "*E. coli* adenylate kinase" has been interpreted as having the amino acid sequence of *E. coli* adenylate kinase as disclosed by Gilles et al. (*Proc Natl Acad Sci, USA* 83:5798-5802, particularly p. 5801; cited in the Office action mailed 1/24/2002). It is noted that the term "Luciola luciferase" encompasses any luciferase from any species of Luciola. As such, no specific sequence can be inferred from this term.

[c] Claim 112 is confusing as being dependent upon canceled claim 106. In the interest of advancing prosecution, the claim has been interpreted as being dependent upon claim 107. It is suggested that applicants clarify the meaning of the claim.

[d] Claims 112, 122, and 130 are unclear in the recitation of "temperature of from 37°C up to the temperature at which the luciferase is denatured." Is the term meant to *encompass* the temperature at which the luciferase is denatured? If so, the method would not achieve the desired result of keeping the luciferase "substantially unaffected." It is suggested that applicants clarify the meaning of the term.

[e] Claim 117 (claims 118-119 dependent therefrom) is drawn to a method for "...producing a recombinant cell according to claim 113..." Claim 113 is drawn to "[a] recombinant *E. coli* cell which has been transformed...so that it expresses adenylate kinase only in a mutated form which is denatured at 37°C" (underline added for emphasis). However, it is noted that the method of claim 117 does not achieve the desired result. While the method of claim 117 achieves transformation of a cell with a vector encoding "adenylate kinase in a form which is denatured at 37°C," there is no

indication that this is the only form of adenylate kinase. In other words, the method of claim 117 produces a recombinant cell that encodes not only thermosensitive adenylate kinase, but also expresses wild-type adenylate kinase. As such, the method of claim 117 does not necessarily produce the cell of claim 113. It is suggested that applicants clarify the meaning of the claim.

[f] Claim 117 (claims 118-119 dependent therefrom) recites the limitation "said conditions." There is insufficient antecedent basis for this limitation in the claim.

[g] Claims 117 (claims dependent therefrom), 125 (claims 126-127 dependent therefrom), and 133 (claims 134-135 dependent therefrom) is unclear in the recitation of "protein product is denatured." Is the "protein product" the adenylate kinase, or some other "protein product" that is produced by the host cell? It is suggested that applicants clarify the claim.

[h] Claims 119 and 134 (claim 135 dependent therefrom) are confusing as the claims recite "[a] method...," however, claims 116 and 131, respectively, from which claims 119 and 134 depend from are drawn to "[a] recombinant cell..." and not a method. In the interest of advancing prosecution, claim 119 has been interpreted as being dependent upon claim 118 and claim 134 has been interpreted as being dependent upon claim 133. It is suggested that applicants clarify the meaning of the claim.

[i] Claims 119, 127, and 135 are indefinite in the recitation of "particular different antibiotic resistance genes" as it is unclear from the claims and the specification as to those *particular* antibiotic resistance genes that are encompassed by the term and

those that are *unparticular* and are not encompassed by the term. It is suggested that applicants clarify the meaning of the term.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claims 108-109, 115-116, and 120-135 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claims 108-109, 115-116, 120 (claim(s) 121-122 dependent therefrom), 123 (claim(s) 124-127 dependent therefrom), 128 (claim(s) 129-130 dependent therefrom), and 131 (claim(s) 132-135 dependent therefrom) recite the limitations "Photinus pyralis

luciferase which has a mutation at position 354," "Luciola luciferase with a mutation at position 354," "Luciola luciferase in which the amino acid at the 217 position is mutated to a hydrophobic amino acid." As support for these limitations, applicants cite documents that are referenced in the specification, namely WO 95/25798 and EP 92110808.0, published as EP-A-524448.

First, it is noted that these references are not properly incorporated by reference ("[m]ere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph.) See MPEP 608.01(p). Second, even assuming arguendo these references have been incorporated by reference, it is noted that the recited limitations are "essential material" for describing the claimed invention and MPEP 608.01(p) states, "[i]n any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to...patents or applications published by foreign countries or a regional patent office." Even assuming arguendo these conditions for proper incorporation by reference were satisfied, it is noted that the examiner can find no disclosure of a Luciola luciferase with a mutation at position 354 in either of the cited references. Applicants are requested to direct the examiner's attention to such support in the original specification, drawings, and claims.

[15] Claims 107-135 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite a genus of E. coli host cells expressing a luciferase that is thermostable at 37°C, optionally wherein the luciferase that is thermostable at 37°C is a Photinus pyralis luciferase that has a mutation at position 354 or a Luciola luciferase with a mutation at position 354 or position 217 and a mutant adenylate kinase that is denatured at 37°C, and optionally wherein the adenylate kinase that is denatured at 37°C includes mutation at amino acid 87 or 107 in the sequence of E. coli adenylate kinase.

The claims are rejected because the structures of the genera of luciferases that are thermostable at 37°C, Photinus pyralis luciferases that have a mutation at position 354, Luciola luciferases with mutation at position 354 or position 217, mutant adenylate kinases that are denatured at 37°C, and E. coli adenylate kinases with mutation at amino acid 87 or 107 have not been adequately described in the specification.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. MPEP § 2163 further states that a representative number of species

means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In this case the specification discloses a prior art reference that describes two representative species of the recited genus of thermostable luciferase polypeptides, i.e., "a thermostable luciferase...as described in European Patent Application No. 92 1 10808.0 or WO 95/25798" (p. 8, lines 19-21). European Patent Application No. 92 1 10808.0, corresponding to European Patent Application Publication 524448 discloses mutant Luciola lateralis luciferase or Luciola cruciata with mutation at position 217 of each of the luciferases. WO 95/25798 (cited in the Office action mailed 1/14/2003) discloses the following representative species of luciferase mutants: Photinus pyralis luciferase with mutation at positions 215 and 354 and Luciola luciferase with mutation at positions 217 and 356. Also, the specification discloses only two representative species of the recited genus of thermosensitive adenylate kinases: "mutation at position 87 in [the sequence of E. coli adenylate kinase] and/or position 107 in the sequence, produces a mutant form of adenylate kinase enzyme which is labile at low temperatures" (p. 5, lines 11-13). The specification fails to describe any additional representative species of the recited genus or even suggest that others were known in the art. In the instant case, the recited genera of thermostable luciferase or thermolabile adenylate kinase polypeptides encompasses species having widely variant structures – including species from any source.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly, (43 USPQ2d 1398). The court in UC California v. Eli Lilly, (43 USPQ2d 1398) held that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the recited genus of thermostable luciferases or thermolabile adenylate kinases of claims 107, 113, and 117, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the polypeptide species within the genus from other polypeptides such that one can visualize or recognize the identity of the members of the genus. Further, while the genus of Photinus pyralis luciferases that have a mutation at position 354, Luciola luciferases with mutation at position 354 or position 217, or E. coli adenylate kinases with mutation at amino acid 87 or 107 have a single amino acid that is shared by all members of the

genus, this structural feature is not a *substantial* structural feature shared by all members of the genus.

Thus, given the lack of description of a representative number of thermostable luciferases and thermolabile adenylate kinases, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that appellant was in possession of the claimed invention.

RESPONSE TO ARGUMENT: Applicants argue the claims would "be recognized by one of ordinary skill as having been described...by the specification." Applicants argue that "[p]roteins described in a manner recited in claim 107 are believed to be known in the art, as listed in the specification and art which has been produced subsequently," citing post-filed references WO 99/14336, WO 01/2002, WO 00/24878, and WO 01/31028.

Applicants' argument is not found persuasive. At least for the reasons of record and the reasons stated above, the specification fails to adequately describe the genus of luciferases that are thermostable at 37°C, Photinus pyralis luciferases that have a mutation at position 354, Luciola luciferases with a mutation at position 354 or position 217, mutant adenylate kinases that are denatured at 37°C, and E. coli adenylate kinases with mutation at amino acid 87 or 107.

Regarding the post-filed references cited by applicants, it is noted that MPEP 608.01(p) states, "[s]ince a disclosure must be complete as of the filing date, subsequent publications or subsequently filed applications cannot be relied on to

establish a constructive reduction to practice or an enabling disclosure as of the filing date."

[16] Claims 107-135 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant E. coli cell transformed with an expression vector encoding mutant E. coli adenylate kinase (according to Gilles et al. as noted above) having mutation at position 87 or 107 and an expression vector encoding a mutant Photinus pyralis luciferase with mutation at position 354 (according to Squirrell et al. as noted above) or a mutant Luciola lateralis or Luciola cruciata luciferase with mutation at position 217 (according to Kajiyama et al.), a method for making said recombinant cell, and a method of using said recombinant cell in the production of luciferase, does not reasonably provide enablement for the broad scope of recombinant cells, methods for making and methods for using as encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir, 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the

predictability or unpredictability of the art, and (8) the breadth of the claims. MPEP § 2164.04 states, "it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed below.

The breadth of the claims: Claims 107 (claim(s) 112 dependent therefrom), 110, 113 (claim(s) 114 dependent therefrom), 117, and 118 (claim(s) 119 dependent therefrom) broadly encompass a recombinant E. coli cell transformed with a nucleic acid encoding any luciferase that is thermostable at 37°C and transformed with a nucleic acid encoding any mutant adenylate kinase that is denatured at 37°C. Claims 108-109, 111, and 115-116 limit the luciferase or adenylate kinase (but not both) to a thermostable mutant Photinus pyralis or Luciola luciferase with mutation at position 354 or a thermostable mutant Luciola luciferase with mutation at position 217 or a mutant E. coli adenylate kinase that include a mutation at position 87 or 107. Claims 120 (claim(s) 121-122 dependent therefrom), 123 (claim(s) 124-127 dependent therefrom), 128 (claim(s) 129-130 dependent therefrom), and 131 (claim(s) 132-135 dependent therefrom) broadly encompass (in relevant part) any species of Luciola luciferase with mutation at position 354 or 217. The scope of the claims is not commensurate with the enablement provided by the disclosure and the prior art with regard to the mutant

luciferases and mutant adenylate kinases broadly encompassed by the claims. In this case, the specification is enabling only for a recombinant E. coli cell transformed with an expression vector encoding mutant E. coli adenylate kinase having a mutation at position 87 or 107 and an expression vector encoding a mutant Photinus pyralis luciferase with mutation at position 354 or a mutant Luciola lateralis or Luciola cruciata luciferase with mutation at position 217.

The state of the prior art and the relative skill of those in the art: At the time of the invention, particular thermostable mutant luciferases were known in the art as evidenced by European Patent Application No. 92 1 10808.0 (cited in the specification at p. 8), corresponding to European Patent Application Publication 524448, which discloses mutant Luciola lateralis luciferase or Luciola cruciata with mutation at position 217 of each of the luciferases and WO 95/25798 (cited in the Office action mailed 1/14/2003), which discloses the following representative species of luciferase mutants: Photinus pyralis luciferase with mutation at positions 215 and 354 and Luciola luciferase with mutation at positions 217 and 356. There is no evidence of record that, at the time of the invention, a thermostable Luciola luciferase having mutation at position 354 was known. Also, certain thermosensitive adenylate kinase mutants were known in the art as evidenced by Gilles et al. (cited by applicants in the specification at p. 4), which discloses a thermosensitive mutant of E. coli adenylate kinase with a mutation at position 87. Methods for manipulating nucleic acids, transforming host cells, and selecting desired transformants by way of a selection marker, e.g., an antibiotic selection marker, were well-known to a skilled artisan. However, the art was not (and

still is not) so developed that a skilled artisan can determine a mutation or mutations a priori in a polypeptide sequence that will impart a desired property, e.g., thermostability or thermosensitivity.

The amount of direction or guidance presented and the presence or absence of working examples: The specification appears to be purely prophetic and fails to disclose an actual working example of the claimed invention. However, the specification discloses specific E. coli adenylate kinase thermosensitive mutants (e.g., p. 7, bottom), i.e., E. coli adenylate kinase having a mutation at position 87 or 107, and cites references that disclose specific thermostable luciferase mutants (p. 8, bottom), i.e., Photinus pyralis luciferase with mutation at position 354 or a mutant Luciola lateralis or Luciola cruciata luciferase with mutation at position 217, and one would have a reasonable expectation of success for generating a recombinant host cell comprising vectors encoding said mutants. However, the cited references do not disclose a thermostable Luciola luciferase having mutation at position 354, and there is no evidence of record that a Luciola luciferase having mutation at position 354 would be thermostable relative to the corresponding wild-type Luciola luciferase. While the specification provides general guidance for generating a mutant polypeptide (p. 4, bottom), there is no specific guidance regarding creation of other mutant luciferase and mutant adenylate kinase polypeptides that are likely to have the desired thermostable or thermosensitive activity.

The predictability or unpredictability of the art: The amino acid sequence of a polypeptide determines the protein's structural and functional properties. Predictability of

which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The high level of unpredictability is also evidenced by Gilles et al. who teach, "a single amino acid substitution may be responsible for changes in protein structure and catalytic activity" (page 5801, left column).

The quantity of experimentation necessary: While recombinant and mutagenesis techniques were known at the time of the invention, it was not routine in the art to screen for all nucleic acids encoding mutant polypeptides as encompassed by the instant claims. In this case, a significant amount of trial and error experimentation is necessary, particularly in view of the lack of guidance, the lack of working examples, and the high level of unpredictability in the art. Such trial and error experimentation was not routine at the time of the invention.

In this case the specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement *In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Applicants argue the claims would "be recognized by one of ordinary skill as having been...enabled by the specification." Applicants argue that "[p]roteins described in a manner recited in claim 107 are believed to be known in the art, as listed in the specification and art which has been produced subsequently," citing post-filed references WO 99/14336, WO 01/2002, WO 00/24878, and WO 01/31028.

Applicants' argument is not found persuasive. At least for the reasons of record and the reasons stated above, the specification fails to enable the full scope of the claimed invention.

Regarding the post-filed references cited by applicants, it is noted that MPEP 608.01(p) states, "[s]ince a disclosure must be complete as of the filing date, subsequent publications or subsequently filed applications cannot be relied on to establish a constructive reduction to practice or an enabling disclosure as of the filing date."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[17] The rejection under 35 U.S.C. 103(a) as being unpatentable over Backman et al. (EP 373962) in view of Kajiyama et al. (*Biochemistry* 32:13795-13799), Gilles et al. (*Proc Natl Acad Sci, USA* 83:5798-5802), and Belinga et al. (*J Chromat A* 695:33-40) is withdrawn. The rejection has been withdrawn solely in view of newly cited references and has not been withdrawn in view of applicants' arguments.

[18] Claims 107-108, 110-115, and 120-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backman et al. (EP 373962; cited in the Office action mailed

11/7/2000) in view of Squirrell (WO 96/02665; referred to herein as "Squirrell (1)"), Squirrell (WO 96/22376; cited in the IDS filed 4/19/2000; referred to herein as "Squirrell (2)"), and Gilles et al. (*Proc Natl Acad Sci, USA* 83:5798-5802; cited by applicants in the specification at p. 4, line 30; cited in the Office action mailed 1/24/2002).

The claims are drawn to a recombinant E. coli cell transformed to express a nucleotide sequence encoding a luciferase that is stable at 37°C, optionally wherein the luciferase is Photinus pyralis or Luciola luciferase with mutation at position 354, and transformed to express adenylate kinase only in mutated form that is denatured at 37°C, optionally wherein the adenylate kinase is E. coli adenylate kinase with mutation at position 87 or 107; a method for making said recombinant cell; and a method for producing luciferase by culturing said cell.

Heat treatment as a form of thermostable polypeptide purification was well-known in the art at the time of the invention. For example, Backman et al. teach the following method: "a method for obtaining a thermostable enzyme essentially free from unwanted contaminants, characterized in comprising the steps of: (a) providing a mesophilic host cell engineered to express a gene encoding a heterologous thermostable enzyme; (b) culturing said mesophilic host cell to produce said thermostable enzyme in a mixture comprising unwanted contaminants; and (c) purifying said thermostable enzyme said purification comprising at least one step in which a mixture comprising said unwanted contaminants is heated to a temperature sufficient to inactivate said unwanted contaminants but not sufficient to inactivate said thermostable enzyme" (column 2, lines 22-37). Backman et al. characterize the contaminating

substances particularly as those that "interfere with the intended use of the enzyme" (column 2, lines 38-43). Backman et al. teach, "[m]esophilic host cells are cells which can be engineered to produce the desired thermophilic enzyme and whose proteins generally are denatured at a temperature that does not denature the desired thermophilic enzyme" (column 2, lines 45-49). Backman et al. do not teach heat purification of luciferase that is thermostable at 37 °C from an adenylate kinase that is denatured at 37 °C.

At the time of the invention, it was well known in the art that adenylate kinase is a contaminant in preparations of luciferase. For example, Squirrell (1) teaches that adenylate kinase is a significant contaminant in a preparation of luciferase (p. 6, top) and that while "[i]t may only be a minor contaminant...its presence in the luciferase may be a limiting factor" for its intended use (p. 7, middle). Squirrell (1) teaches that a suitable method for purifying luciferase from adenylate kinase is "ageing for a period at elevated ambient temperature" (underline added for emphasis; p. 8, top).

Squirrell (2) teaches E. coli-compatible expression vectors encoding a thermostable Photinus pyralis luciferase with mutation at position 354.

Gilles et al. teach thermosensitive E. coli mutants comprising a mutation in the endogenous *adk* gene encoding adenylate kinase (page 5798, left column, middle). Characterization of the mutant adenylate kinase protein revealed the presence of a substitution of serine for proline at amino acid position 87 (page 5798, right column, top). Gilles et al. teach thermosensitive adenylate kinase is irreversibly inactivated at 40 degrees Celsius due to proteolysis subsequent to thermal denaturation (page 5798, left

column, bottom) and that this increased susceptibility to proteolysis is enhanced by increased temperature (page 5801, right column, middle). Gilles et al. teach that an analysis of purified wild-type and mutant adenylate kinase indicated that the mutant loses significant enzyme activity as the reaction temperature is increased from 27 degrees Celsius to 40 degrees Celsius (page 5802, Table 4) and that these changes in kinetic parameters of the mutant are most likely due to destabilization of the protein molecule which is enhanced by increased temperature (page 5802, left column, top). It should be noted that the claims require that the *E. coli* host be "transformed...so that it expresses adenylate kinase only in a mutant form." In this case, the examiner has broadly interpreted the term "transformed" to encompass "changed" or "mutated," in accordance with MPEP 2111. Thus, there is no requirement that the host cell be "transformed" with a vector encoding a mutant adenylate kinase.

At the time of the invention, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Backman et al., Squirrell (1), Squirrell (2), and Gilles et al. to transform the mutant *E. coli* of Gilles et al. with the vector encoding a thermostable luciferase of Squirrell (2), express the mutant thermostable luciferase, heat the resulting cell culture or extract at a temperature sufficient to denature adenylate kinase and optionally purify the expressed thermostable luciferase. One would have been motivated to do this because of Backman et al., which teaches a method for heat purifying a thermostable protein from a thermolabile contaminant and Squirrell (1), which teaches that adenylate kinase is a contaminant of luciferase and should be removed from preparations of luciferase and that luciferase

can be purified from adenylate kinase by "ageing for a period at elevated ambient temperature." One would have a reasonable expectation of success for practicing the claimed method because of the results of Backman et al., Squirrell (2), Gilles et al., and Squirrell (1). Therefore, claims 107-108, 110-115, and 120-124 drawn to a recombinant cell and methods of making and use thereof as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[19] Claims 117-119 and 125-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backman et al. in view of Squirrell (1), Squirrell (2), and Gilles et al. as applied to claims 107-108, 110-115, and 120-124 above, and further in view of Novagen 1997 Catalog (pp. 41-45) and Kiel et al. (Mol Gen Genet 207:294-301; cited in the Office action mailed 11/7/2000).

The claims are drawn to a method for making a recombinant E. coli cell transformed with a vector expressing a mutant adenylate kinase in a form that is denatured at 37°C, optionally having a selection marker and further transformed with a vector encoding a thermostable luciferase, optionally wherein the luciferase is Photinus pyralis or Luciola luciferase with mutation at position 354, and optionally wherein the vector comprises a different selection marker.

The teachings of Backman et al., Squirrell (1), Squirrell (2), and Gilles et al. are described above. None of the cited references teaches transforming an E. coli host with a vector encoding a mutant adenylate kinase optionally comprising a selection marker.

Novagen 1997 Catalog teaches an expression system, which is "the most powerful system yet developed for the cloning and expression of recombinant proteins

in *E. coli*" (p. 42, top). The expression system uses a pET vector and a compatible *E. coli* host cell, e.g., BL21 (p. 42-43) and Kiel et al. (Mol Gen Genet 207:294-301; cited in the Office action mailed 11/7/2000).

Also, at the time of the invention, methods for disrupting an endogenous gene in the chromosome of E. coli was known in the art as exemplified by Kiel et al. Kiel et al. disclose the disruption of the endogenous glycogen branching enzyme or beta-galactosidase gene of *E. coli* using an insertion vector comprising a kanamycin antibiotic selection marker to select for those mutants having a disrupted gene.

At the time of the invention, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Backman et al., Squirrell (1), Squirrell (2), Gilles et al., Novagen 1997 Catalog, and Kiel et al. to disrupt the endogenous adenylate kinase gene of E. coli strain BL21 by homologous recombination using a vector comprising a first antibiotic selection marker, transform the resulting mutant BL21 strain with a pET vector encoding the thermostable luciferase of Squirrell (2) comprising a second antibiotic selection marker, e.g., ampicillin, to select for those transformants that comprise the pET vector and use the resulting transformant to produce luciferase followed by purification by the method of Backman et al. One would have been motivated to do this in order to produce a large amount of luciferase using "the most powerful system yet developed for the cloning and expression of recombinant proteins in *E. coli*." One would have a reasonable expectation of success for making such a recombinant cell because of the results of Squirrell (2), Gilles et al., Kiel et al., and Novagen 1997 Catalog. Therefore, claims 117-119 and 125-127 drawn to a method

for making a recombinant cell as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

[20] Claims 107, 109-114, 116, and 128-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backman et al. in view of Squirrell (1), Kajiyama et al. (*Biochemistry* 32:13795-13799), and Gilles et al.

The claims are drawn to a recombinant E. coli cell transformed to express a nucleotide sequence encoding a luciferase that is stable at 37°C, optionally wherein the luciferase is Luciola luciferase with mutation at position 217, and transformed to express adenylate kinase only in mutated form that is denatured at 37°C, optionally wherein the adenylate kinase is E. coli adenylate kinase with mutation at position 87 or 107; a method for making said recombinant cell; and a method for producing luciferase by culturing said cell.

The teachings of Backman et al., Squirrell (1), and Gilles et al. are described above. As noted above, Backman et al. does not teach heat purification of luciferase that is thermostable at 37 °C from an adenylate kinase that is denatured at 37 °C.

Kajiyama et al. teach E. coli-compatible expression vectors encoding a thermostable Luciola cruciata luciferase with mutation at position 217.

At the time of the invention, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Backman et al., Squirrell (1), Kajiyama et al., and Gilles et al. to transform the mutant *E. coli* of Gilles et al. with the vector encoding a thermostable luciferase of Kajiyama et al., express the mutant thermostable luciferase, heat the resulting cell culture or extract at a temperature

sufficient to denature adenylate kinase and optionally purify the expressed thermostable luciferase. One would have been motivated to do this because of Backman et al., which teaches a method for heat purifying a thermostable protein from a thermolabile contaminant and Squirrell (1), which teaches that adenylate kinase is a contaminant of luciferase and should be removed from preparations of luciferase and that luciferase can be purified from adenylate kinase by "ageing for a period at elevated ambient temperature." One would have a reasonable expectation of success for practicing the claimed method because of the results of Backman et al., Kajiyama et al., Gilles et al., and Squirrell (1). Therefore, claims 107, 109-114, 116, and 128-132, drawn to methods and host cells as described above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[21] Claims 117-119 and 133-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backman et al. in view of Squirrell (1), Kajiyama et al., and Gilles et al. as applied to claims 107, 109-114, 116, and 128-132 above, and further in view of Novagen 1997 Catalog (pp. 41-45) and Kiel et al. (Mol Gen Genet 207:294-301; cited in the Office action mailed 11/7/2000).

The claims are drawn to a method for making a recombinant E. coli cell transformed with a vector expressing a mutant adenylate kinase in a form that is denatured at 37°C, optionally having a selection marker and further transformed with a vector encoding a thermostable luciferase, optionally wherein the luciferase is Luciola luciferase with mutation at position 217, and optionally wherein the vector comprises a different selection marker.

The teachings of Backman et al., Squirrell (1), Kajiyama et al., and Gilles et al. are described above. None of the cited references teaches transforming an E. coli host with a vector encoding a mutant adenylate kinase optionally comprising a selection marker.

Novagen 1997 Catalog teaches an expression system, which is "the most powerful system yet developed for the cloning and expression of recombinant proteins in *E. coli*" (p. 42, top). The expression system uses a pET vector and a compatible *E. coli* host cell, e.g., BL21 (p. 42-43).

Also, at the time of the invention, methods for disrupting an endogenous gene in the chromosome of E. coli was known in the art as exemplified by Kiel et al. Kiel et al. disclose the disruption of the endogenous glycogen branching enzyme or beta-galactosidase gene of *E. coli* using an insertion vector comprising a kanamycin antibiotic selection marker to select for those mutants having a disrupted gene.

At the time of the invention, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Backman et al., Squirrell (1), Kajiyama et al., Gilles et al., Novagen 1997 Catalog, and Kiel et al. to disrupt the endogenous adenylate kinase gene of E. coli strain BL21 by homologous recombination using a vector comprising a first antibiotic selection marker, transform the resulting mutant BL21 strain with a pET vector encoding the thermostable luciferase of Kajiyama et al. comprising a second antibiotic selection marker, e.g., ampicillin, to select for those transformants that comprise the pET vector and use the resulting transformant to produce luciferase followed by purification by the method of Backman et al. One would

have been motivated to do this in order to produce a large amount of luciferase using "the most powerful system yet developed for the cloning and expression of recombinant proteins in *E. coli*." One would have a reasonable expectation of success for making such a recombinant cell because of the results of Kajiyama et al., Gilles et al., Kiel et al., and Novagen 1997 Catalog. Therefore, claims 117-119 and 133-135, drawn to a method for making a recombinant cell as described above would have been obvious to one of ordinary skill in the art at the time of the invention.

[22] RESPONSE TO ARGUMENT: To the extent applicants' argument applies to the new rejection under 35 U.S.C. 103(a), the argument is addressed below.

Applicants argue EP-373962 (Backman et al.) is not concerned with luciferase production and describes production of thermostable proteins in mesophilic host cells. According to applicants, the thermostable protein products can be purified by heating to temperatures under which all other host cell proteins are denatured. Applicants argue this teaching lacks suggestion to modify the thermolability of a contaminating protein. Applicants argue the reference does not suggest the invention or motivate one to practice the invention because the thermostable proteins are so temperature stable that they may be safely heated to temperatures, e.g., 70 degrees Celsius, which all other host cell proteins are denatured.

Applicants' argument is not found persuasive. As noted above, Backman et al. disclose the following method: "a method for obtaining a thermostable enzyme essentially free from unwanted contaminants, characterized in comprising the steps of: (a) providing a mesophilic host cell engineered to express a gene encoding a

heterologous thermostable enzyme; (b) culturing said mesophilic host cell to produce said thermostable enzyme in a mixture comprising unwanted contaminants; and (c) purifying said thermostable enzyme said purification comprising at least one step in which a mixture comprising said unwanted contaminants is heated to a temperature sufficient to inactivate said unwanted contaminants but not sufficient to inactivate said thermostable enzyme" (column 2, lines 22-37). While it is acknowledged that Backman et al. teach a working example of their method using a highly thermostable polymerase enzyme. However, there is no teaching in Backman that would teach away from applying their method to any thermostable protein that can be heat purified at any temperature – from extreme to not so extreme – from a contaminating protein, including a thermostable luciferase. The examiner acknowledges that the reference of Backman et al. – by itself – does not expressly teach modifying a contaminating protein to make it more thermolabile. However, it is the examiner's position that the combination of references clearly teaches such a modification.

Applicants next address the reference of Kajiyama et al. While this reference is not cited in the instant rejection, to the extent the reference of Lowe is similar to Kajiyama et al. in its teachings, applicants arguments have been addressed herein.

Applicants argue the thermostable luciferase of Kajiyama could not be applied to the method of EP-373962 because the thermostable luciferase of Kajiyama et al. loses 70% of its activity at 50 degrees Celsius over 40 minutes and, in view of this loss of activity, an ordinarily skilled artisan would not have been motivated to use the high temperatures of the method of EP-373962 to purify the luciferase of Kajiyama et al. as,

according to applicants, there would have been no reasonable expectation of success for obtaining an active product.

Applicants' argument is not found persuasive. It is noted that, while the working example of Backman et al. teaches the use of relatively high temperatures, the general method disclosed by Backman et al. does not teach the use of *any* particular temperature. Thus, a skilled artisan, would have recognized that the temperature used in the working example of Backman et al. would have resulted in denaturation of even a thermostable luciferase, would not have used such a relatively high temperature as in the working example of Backman. Instead, an ordinarily skilled artisan would have recognized that one need only apply a temperature sufficient to denature adenylate kinase for a time that does not substantially inactivate thermostable luciferase. The reference of Gilles et al. specifically teaches that the mutant adenylate kinase is denatured at 40°C and the reference of Kajiyama et al. discloses that the mutant thermostable luciferase maintained "over 75%" of the initial activity after 10 minutes at 50°C (p. 13797, right column, bottom), i.e., the luciferase mutant is "substantially unaffected" in accordance with the claimed methods. As such, one of ordinarily skill in the art, in view of the teachings of the prior art, would have used only a temperature or temperatures appropriate for maintaining activity thermostable luciferase, while denaturing thermosensitive adenylate kinase.

Applicants argue the references of Gilles et al. and Belinga et al. have been combined in hindsight as neither of the references are related to recombinant protein expression. According to applicants, Gilles et al. discloses "certain mutations [that] led

to mutants where the adenylate kinase was more thermolabile than in the wild type" and do not teach the use of this mutant as an expression host. Applicants argue Belinga et al. teaches that, while adenylate kinase is a contaminant of luciferase, the reference teaches removal of adenylate kinase by conventional column chromatography and does not motivate one to remove this contaminant by using an engineered host cell.

Applicants' argument is not found persuasive. In response to applicants' argument regarding combining the references in hindsight, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In this case, the teachings of Gilles et al. and Squirrell (1) were disclosed in the prior art and were "within the level of ordinary skill at the time the claimed invention was made."

Regarding the reference of Gilles et al., the examiner acknowledges that Gilles et al. do not teach the use of their mutant *E. coli* expressing a thermosensitive adenylate kinase as a host cell for recombinant protein expression. However, in view of the combination of references, particularly the teachings of Backman et al., one would have recognized the use of this mutant for recombinant expression of thermostable luciferase for subsequent heat inactivation of adenylate kinase according to the method of Backman et al.

Regarding the reference of Belinga et al., it is noted that the reference of Belinga et al. is not cited in the instant rejection in favor of the reference of Squirrell (1), which also teaches purification of luciferase using column chromatography and further teaches purification of luciferase from adenylate kinase by "ageing for a period at elevated ambient temperature" (underline added for emphasis; p. 8, top).

It is noted that applicants have chosen to attack the cited references individually instead of attacking the *combination* of references. In this case, the rejection is based on a combination of references – not a single reference – and it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

[23] Status of the claims:

Claims 107-135 are pending.

Claims 107-135 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and alternate Fridays from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

04-29-05

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER